REMARKS

Claims 1, 3-14, 22, 23, and 28 are pending in the application. Claims 14, 22, and 23 were withdrawn from consideration, leaving claims 1, 3-13, and 28 subject to examination. Claims 1, 6, and 8-13 are rejected under 35 U.S.C. § 102(e), and claims 1, 3-9, and 28 are rejected under 35 U.S.C. § 103(a). Each of the rejections is addressed below.

First, Applicants note that the status indicators for claims 14, 22, and 23 have been changed to indicate that these claims have been withdrawn, consistent with the Examiner's suggestion. Applicants request, however, that rejoinder of these claims be reconsidered. Claims 14, 22, and 23 were previously indicated as being in a different restriction group (Group II) from that elected for examination (Group I) in view of US 2002/0071832. Applicants respectfully submit that the claims of Groups I and II define a technical feature linking the inventions of these groups, which defines a contribution over US 2002/0071832. This is discussed in more detail below in connection with the rejections based on the cited reference, over which the present invention is novel and inventive, thus defining a contribution over the prior art. Applicants thus request rejoinder of the claims of Groups I (claims 1-13) and II (claims 14, 22, and 23), which are readable on the elected species.

The rejections in the Office Action are each addressed, as follows.

Rejection under 35 U.S.C. § 102(e)

Rejection over Fong et al., US 2002/0071832

Claims 1, 6, and 8-13 remain rejected under 35 U.S.C. § 102(e) as being anticipated by Fong et al., US 2002/0071832. In response to Applicants' prior submissions that the present

invention provides a new use for a known method, the Examiner states "regardless of what Fong et al. intended to be the end result, Fong et al. teach the claimed method steps" and "the fact that the same method steps have other, not-yet-known effects anticipate the claimed invention. See MPEP 2112. This is because any of the effects caused by the method described by Fong et al. are inherent to the method." Applicants respectfully request that this rejection be withdrawn for the following reasons.

Applicants first note that claim 1 has been amended to specify that the subject is in need of treatment of metastasis of cancer at a site distal to the site of surgical resection of a tumor from the subject. Such first line treatment of metastases in these subjects is supported throughout the application. For example, at page 2, lines 9-12, the specification states:

> The administered herpes virus prevents or treats the recurrence of any cancer that may remain at the site of resection, as well as prevents or treats any cancer that may have metastasized from the site of surgical resection. The metastasized cancer may be found in the lymphatic system, for example, in a lymph node.

Additional support for this concept can be found at page 2, lines 25-30 of the application:

> Thus, the methods of the invention can be used to treat primary tumors, *as well as to prevent lymphatic metastases*. The herpes viruses administered according to the methods of the invention follow the same pathways as metastasizing tumor cells, thus *enhancing the likelihood of their reaching those areas within the lymphatic system, e.g., lymph nodes, that are at greatest risk for harboring metastatic disease*. (Emphasis added.)

In addition, at page 3, lines 5-7 the application states:

> The invention thus provides targeted, safe, and effective methods for preventing and treating primary site cancer recurrences, *as well as regional lymphatic metastases*. (Emphasis added.)

Further, Figure 7 and the corresponding text (see page 12, line 12 through page 13, line 7) describe experiments showing the efficacy of such methods. In particular, these passages show

that in a control group (PBS injected) 17.9% of the animals developed palpable nodal metastases, whereas in the treatment group (NV1023) only 3.5 % developed a palpable nodal metastasis, and that disease free survival was significantly enhanced.

Fong does not teach the treatment of subjects such as those now specified in the present claims, which are in need of treatment of metastasis of cancer at a site distal to the site of surgical resection of a tumor. Rather, Fong suggests inoculation of viruses into resected tumor beds to destroy tumor cells remaining in the tumor beds. The methods of the present invention are thus not inherent in the method of Fong. Whether a virus administered according to the method of Fong may travel to a distal site does not matter, as Fong does not teach administration of virus to tumor beds of subjects needing treatment at a distal site. The presently claimed invention thus represents a new use of the application of virus to sites of tumor resection.

In the event that the Examiner considers the present subjects to be a species of the genus of cancer patients, as taught by Fong, Applicants respectfully submit that a genus does not anticipate a species. This notwithstanding, it is clear from Fong that the goal of the treatment is to kill cells at the site of resection. Applicants thus request that this rejection be withdrawn.

In response to the Examiner's statement that "Fong et al.'s process always had the ability to treat metastatic cells, whether or not Fong et al. realized it at the time of publication," Applicants submit that Fong did not teach using their process with subjects as now specified in the present claims and, thus, practice of the method of Fong does not inherently result in the practice of the method of the present claims.

The Examiner comments on Applicants' prior submission that the methods of the present claims provide treatment options for subjects for whom treatment regimens based solely on

surgical excision of tumors and destruction of tumor cells in the tumor bed would not have been considered sufficient (e.g., tumors found to have metastasized or tumors having a high propensity to metastasize). In particular, the Examiner states "this is not persuasive, because claim 1 [is] drawn to a method of treating metastases by administering herpes virus to the site of surgical resection. If Applicant indicates that it is not effective to treat metastases by focusing only on the site of excision, then claim 1 is not enabled."

In response, Applicants submit that the method of Fong was not taught to be carried out with the subjects specified in the present claims and, thus, as submitted previously, the presently claimed method provides a new approach for treating subjects as noted above (e.g., subjects with tumors found to have metastasized or having a high propensity to metastasize). There is no issue as to enablement of claim 1. Rather, the method of Fong does not anticipate the present claims as it is not taught to be carried out with the subjects of the present claims.

Further in this rejection, the Examiner comments on a statement in the specification that "this study investigates the use of an attenuated, replication-competent, oncolytic herpes simplex virus (NV1023), both to treat a primary tumor by direct injection, and to travel through the lymphatic system to treat metastatic tumors within the lymph nodes draining lymph from the site of primary cancer (specification, page 10)." In particular, the Examiner notes that this statement indicates "the treatment of primary cancer by direct injection must also treat metastatic cancer in the lymph nodes. If it is not effective to treat metastases by focusing only on the site of excision, then the specification does not provide an enabling disclosure."

In response, Applicants first submit that the quoted statement, when read in context, clearly is mentioning two separate methods: (i) direct tumor injection, and (ii) administration

resulting in travel through the lymphatic system. This is shown, for example, by the separate descriptions of these approaches on page 12, lines 5-10 ("Viral Therapy of SCC VII Auricular Tumors"; describes direct injection approach) and page 12, line 12 through page 13, line 7 ("Viral Therapy of SCC VII Cervical Metastases"; describes administration to surgical bed after excision).

Applicants further submit that, as discussed above, the presently claimed invention is directed towards the treatment of subjects in need of treatment of metastasis of cancer at a site distal from the site of surgical resection. Applicants have not stated that it is not effective to focus only on the site of excision as the site of administration but, rather, based on the prior art, administration to such a site would not have been considered to be effective for the treatment of metastases, and thus would not have been used with the patients now specified in the claims.

Further in the rejection, the Examiner comments on Applicants' prior submissions concerning the nature of the targeted cells of the claimed methods and that of the cells of Fong. To provide clarification on this matter, Applicants submit that it appears from the statement of Fong concerning administration of virus to surgical beds that the type of cell targeted is a cell that has the potential to grow at the site of the surgical bed, and not cells that may have already traveled from the surgical bed. This is because Fong states that his method is carried out "to ensure destruction of any remaining tumor cells" (i.e., cells remaining at the tumor bed). The position that such cells were the focus of the statement of Fong is reasonable, given that most cells in a tumor do not have metastatic potential (as supported in the prior Reply and prior cited references). As discussed above and elsewhere herein, it was not until the present invention that it became known that cells already traveling from the resection site, such as through the

lymphatic system, can be targeted by administration to a surgical bed. The Examiner comments that the cells of the examples of Fong (OCUM-2MD3 cells) are metastatic. In response, Applicants note that, in the *in vivo* experiments employing these cells, virus was administered intraperitoneally and not to a surgical bed. Thus, the nature of these cells (OCUM-2MD3) is not relevant to the present rejection.

In view of the above, Applicants submit that the present invention provides a new use of a known process and, because such methods are patentable subject matter (see, e.g., 35 U.S.C. § 101; *In re King*, 801 F.2d 1324 (Fed. Cir. 1986); and *Perricone v. Medicis Pharmaceutical Corp.*, 432 F.3d 1368 (Fed. Cir. 2005)), Applicants respectfully request that this rejection be withdrawn.

Rejections under 35 U.S.C. § 103(a)

Rejection over Fong et al., US 2002/0071832, in view of Wong et al., Human Gene Therapy 12(3):253-265, 2001

Claims 1, 6, and 7 were rejected for obviousness over Fong et al., US 2002/0071832, in combination with Wong et al., Human Gene Therapy 12(3):253-265, 2001. This rejection is respectfully traversed.

As discussed above in detail with respect to the rejection under 35 U.S.C. § 102(e), the present claims have been amended to specify the treatment of subjects in need of treatment of metastasis of cancer at a site distal to the site of surgical resection of a tumor, and Fong does not teach the treatment of such subjects. In particular, as discussed above, the focus of Fong is the destruction of tumor cells at the site of resection. It was not known prior to the present invention

that virus administered to a surgical bed could travel through the lymphatic system to destroy metastatic cells and, thus, there would have been no motivation, based on Fong, to use such an approach to treat subjects with tumors found to have metastasized or tumors having a high propensity to metastasize. Thus, Fong does not provide any suggestion or motivation to carry out the presently claimed invention. Such a suggestion or motivation also does not come from Wong, which was cited as describing a particular attenuated, replication-competent, oncolytic herpes simplex virus, NV1023.

In view of the above, Applicants respectfully request that the rejection under 35 U.S.C. § 103(a) over the Fong and Wong publications be withdrawn.

Rejection over Kooby et al., FASEB J. 13:1325-1334, 1999, in view of Rodgers and McCall, Brit. J. Surg. 87:1142-1155, 2000

Claims 1, 3-6, 8, 9, and 28 are newly rejected for obviousness over Kooby et al., FASEB J. 13:1325-1334, 1999, in view of Rodgers and McCall, Brit. J. Surg. 87:1142-1155, 2000. This rejection is respectfully traversed, for the reasons discussed below.

Kooby is cited for teaching that portal infusion of G207 in a rat model of hepatic micrometastasis resulted in fewer nodules than PBS-treated rats. The Examiner notes that Kooby teaches that the best treatment for colorectal cancer patients having liver metastases is resection of the liver, that such patients often experience recurrence, likely due to microscopic residual disease, and that herpes virus therapy can be used to improve outcome in these cases. Based on this, the Examiner states that it would have been obvious to resect metastatic tumors in the livers of patients and to administer G207 to the sites of resection. Applicants respectfully disagree.

The focus of Kooby with respect to liver metastases of colon cancer is administration of herpes virus by infusion, which results in the virus being delivered throughout the liver. Kooby provides no suggestion or motivation to apply virus to the site of resection. Further, when mentioning the possibility of using the approach in conjunction with surgical resection, Kooby notes that the treatment is to reduce local recurrence. This is shown, for example, at page 1332, where Kooby states:

> In addition to examining direct intratumoral injections, we investigated the efficacy of G207 as a possible agent for regional antineoplastic therapy. *Introducing the virus by selective intravascular infusion is appealing since it allows a diffuse distribution of virus within the tumor*... Our results suggest that *regional infusion with G207* may be valuable for treatment of unresectable liver malignancies or *may be useful as an adjuvant to surgical resection to reduce postoperative local recurrence*. (Emphasis added.)

Given the fact that Kooby has proposed a solution for the possibility of the presence of residual disease after resection (infusion leading to diffuse viral distribution), which appears to provide therapeutic benefit, there would not have been motivation, based on Kooby, for those of skill in the art to consider another approach to dealing with the problem of residual disease. Further, even if those of skill in the art wanted to supplement the approach of Kooby in this regard, there is not any teaching in Kooby that would indicate that virus administered at the site of resection would travel to any loci of metastases. Thus, although, as noted by the Examiner, Kooby indeed does teach that administration of G207 can be used to improve outcome for patients having residual disease following resection, Kooby also teaches that this solution is carried out by infusion and provides evidence that this approach is beneficial. There would therefore be no motivation to consider another approach at all, not to mention that of the present invention.

The Rodgers reference is cited for teaching that colorectal cancer can have metastases in hepatic lymph nodes. With respect to this reference, the Examiner states: "given that the steps taught by Kooby et al. are the same as those of the claims, an artisan would have arrived at the claimed invention of treating metastases in lymph nodes." Applicants respectfully disagree.

First, as is noted above, the methods of the claimed invention differ from that of Kooby. For example, Kooby nowhere suggests or provides motivation to administer a virus to the site of surgical resection, so that the virus can travel to a site of metastasis. Rather, Kooby teaches the administration of virus by infusion, which results in diffuse distribution of the virus throughout the liver. Thus, regardless of the teachings of Rodgers that the liver includes lymph nodes, none of the cited references teach or suggest what is claimed. Applicants thus request that this rejection be withdrawn.

Applicants finally submit that, notwithstanding the Examiner's conclusions with respect to the rejections based on the Fong reference, claims 3-5 and 28 have only been rejected over the Kooby and Rodgers references. Thus, Applicants respectfully request separate consideration of these claims in connection with this rejection.

In view of the above, Applicants respectfully request the rejection over the Kooby and Rodgers reference be withdrawn.

CONCLUSION

Applicants submit that the claims are in condition for allowance, and such action is respectfully requested. Although no charges are believed to be due, if there are any charges or any credits, please apply them to Deposit Account No. 03-2095.

Respectfully submitted,

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